Ebola Neurological Presentation: Encephalitis or Encephalopathy Consequences for Management

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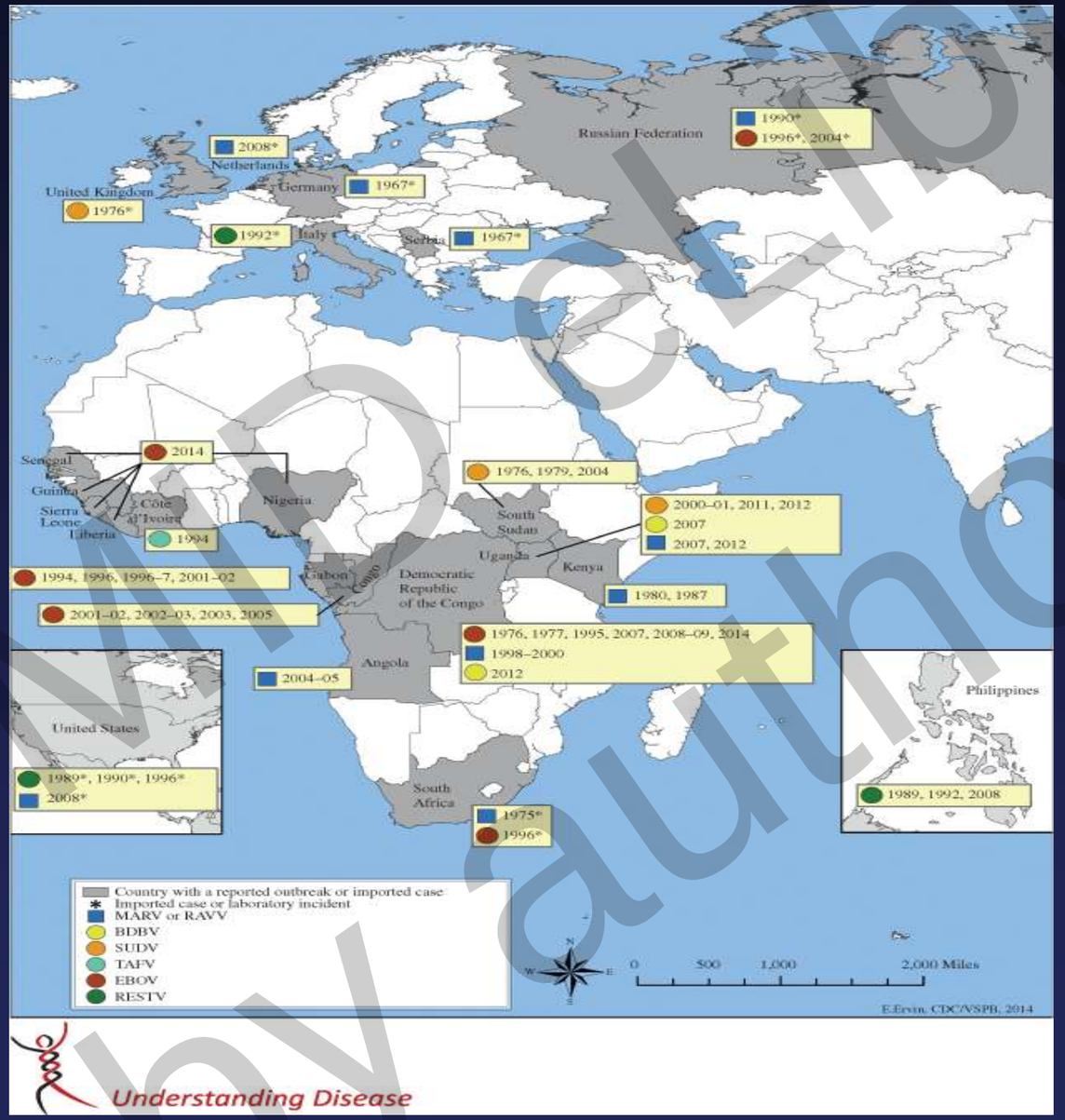
Filovirus Chronologic Hx and Map

Zaire EBOV-
Makona variant

Lomela variant



The Journal of Pathology
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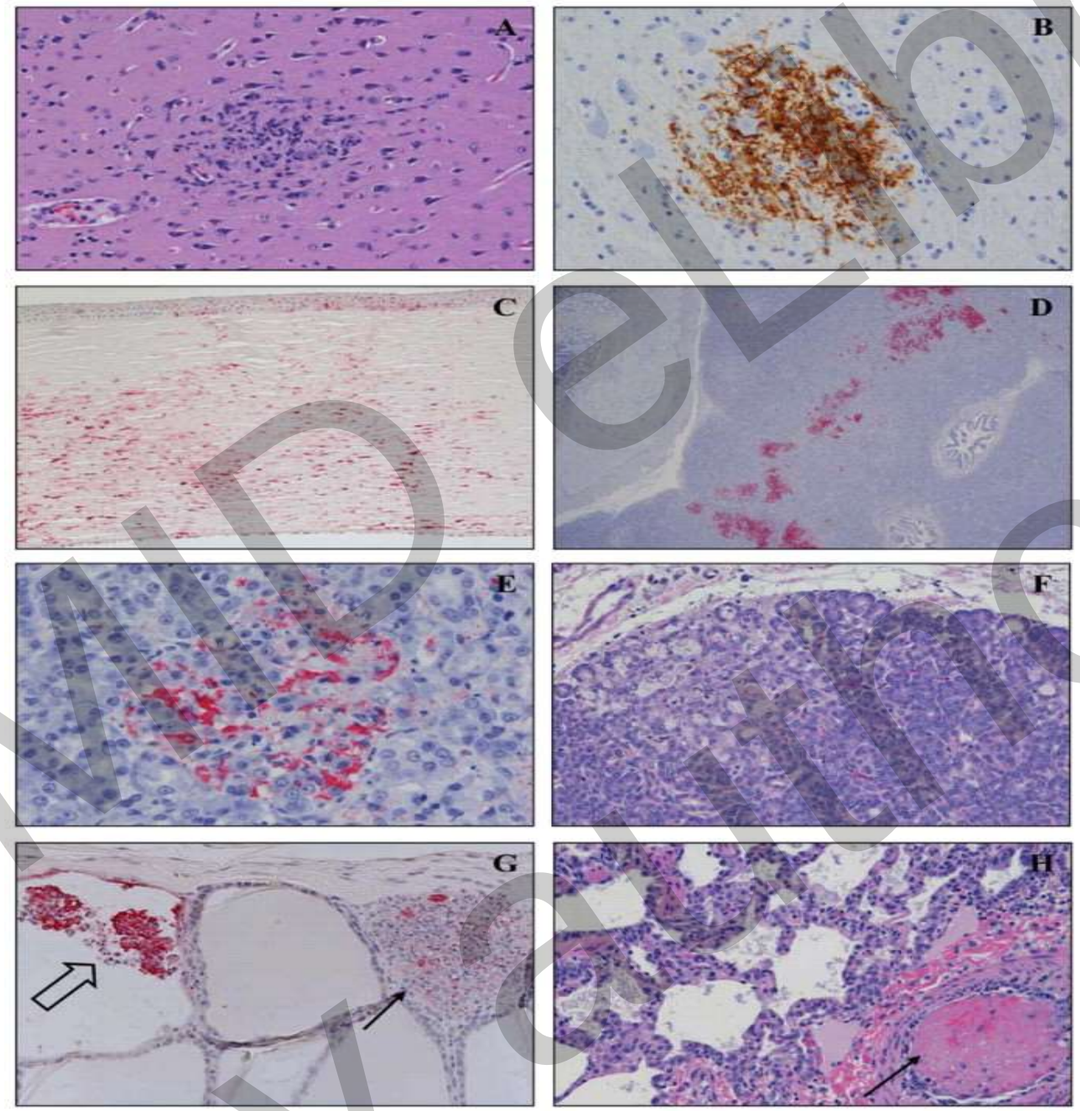
http://onlinelibrary.wiley.com/doi/10.1002/path.4456/full#path4456-fig-0002

History of Neurology in Ebola and Marburg

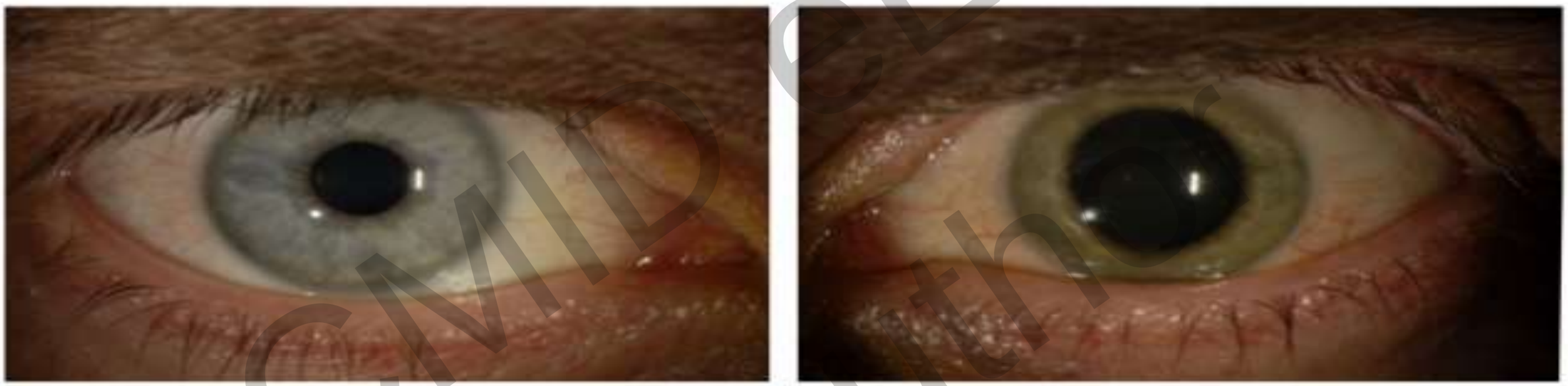
- Marburg 1967 myalgias, weakness, paresthesias, limb pain, restless legs, myelitis, meningitis HA CSF 0-24 WBC, prot 0.68 gm/l, “clouded consciousness”, encephalitis- “disturbed consciousness” for 6 and 10 days: post-mortem widely distributed microglial nodules, diffuse glial proliferation, perivascular lymphocytic inflammatory changes, scattered petechial hemorrhages / dying after 1 day of coma- vascular congestion and RBC extravasation (Bechtelsheimer 1969, Jacob 1971)
- Marburg- Joburg 1975 uveitis 2 mo after hospital d/c, virus cultured from anterior chamber of eye (Geer 1975)
- Ebola Z- Kikwit 1995 HA (85%,95%), lumbar pain, hearing loss (5,11%), tinnitus, dysesthesias (0,5%), convulsions (2%,0), late manifestations: conjunctivitis, uveitis, unilateral visual loss, hearing loss or tinnitus, asthenia (85%, 95%) fatal, survived (Bwaka 1999)
- Ebola Z-SL (Kenema) 2014 HA (80%), weakness dizziness (70%) conjunctivitis confusion (30%), hearing loss (8%), convulsions (5%) fatal cases (Schieffelin 2014)
- Post-Ebola syndrome “when its over its not over” (eye problems: retroorbital pain, vis loss, hearing loss, body aches, chest pain, HA, fatigue, memory loss, sleep disturbance, psych)
- No brain postmortem on EBOV human cases
- Ebola Z-NHP glial nodules and/or meningoencephalitis, viral antigen detected in inflammatory foci or bland neuropil (Larsen 2007)

Tissue pathology of rhesus macaques infected with Zaire Ebola virus.



Thomas Larsen et al. J Infect Dis. 2007;196:S323-S328

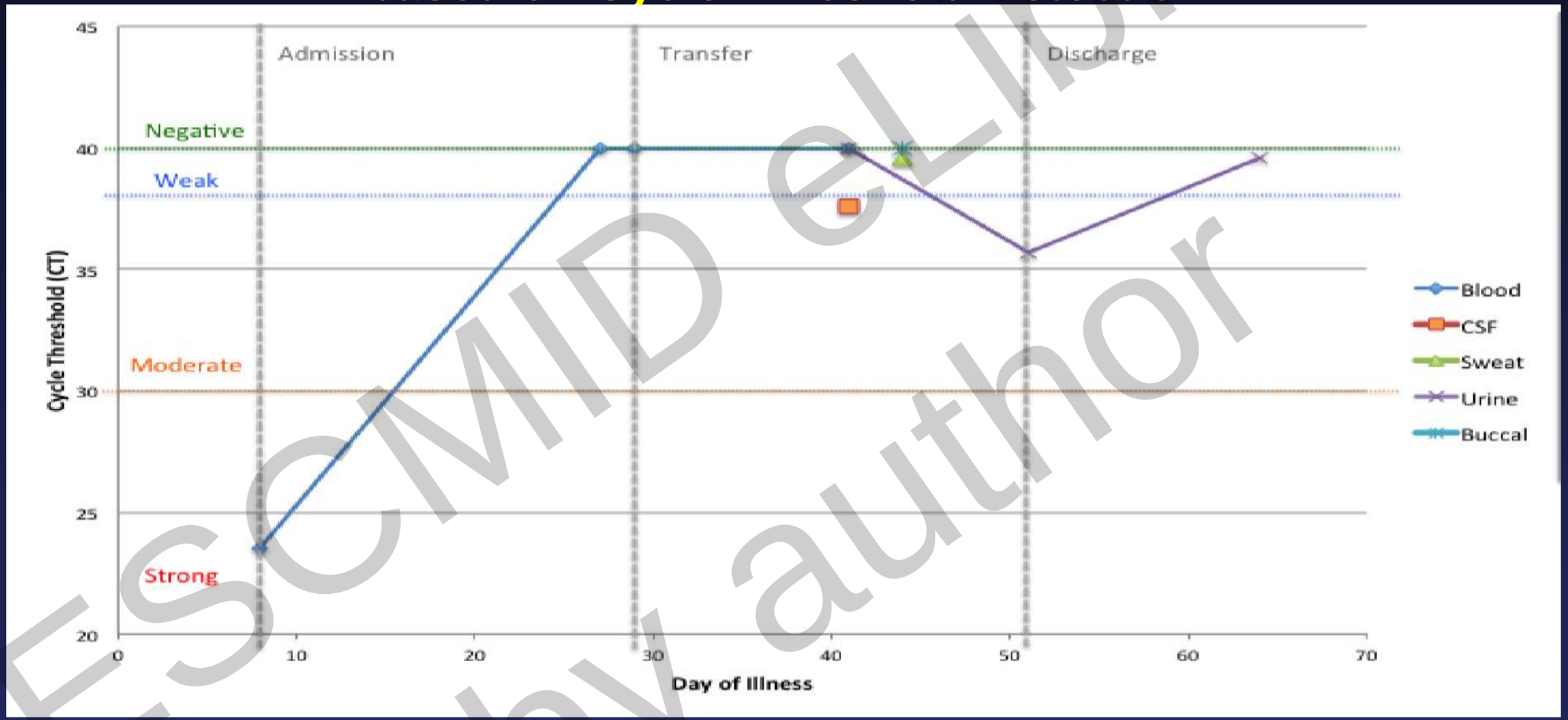
The Journal of Infectious Diseases



Case 1 Summary

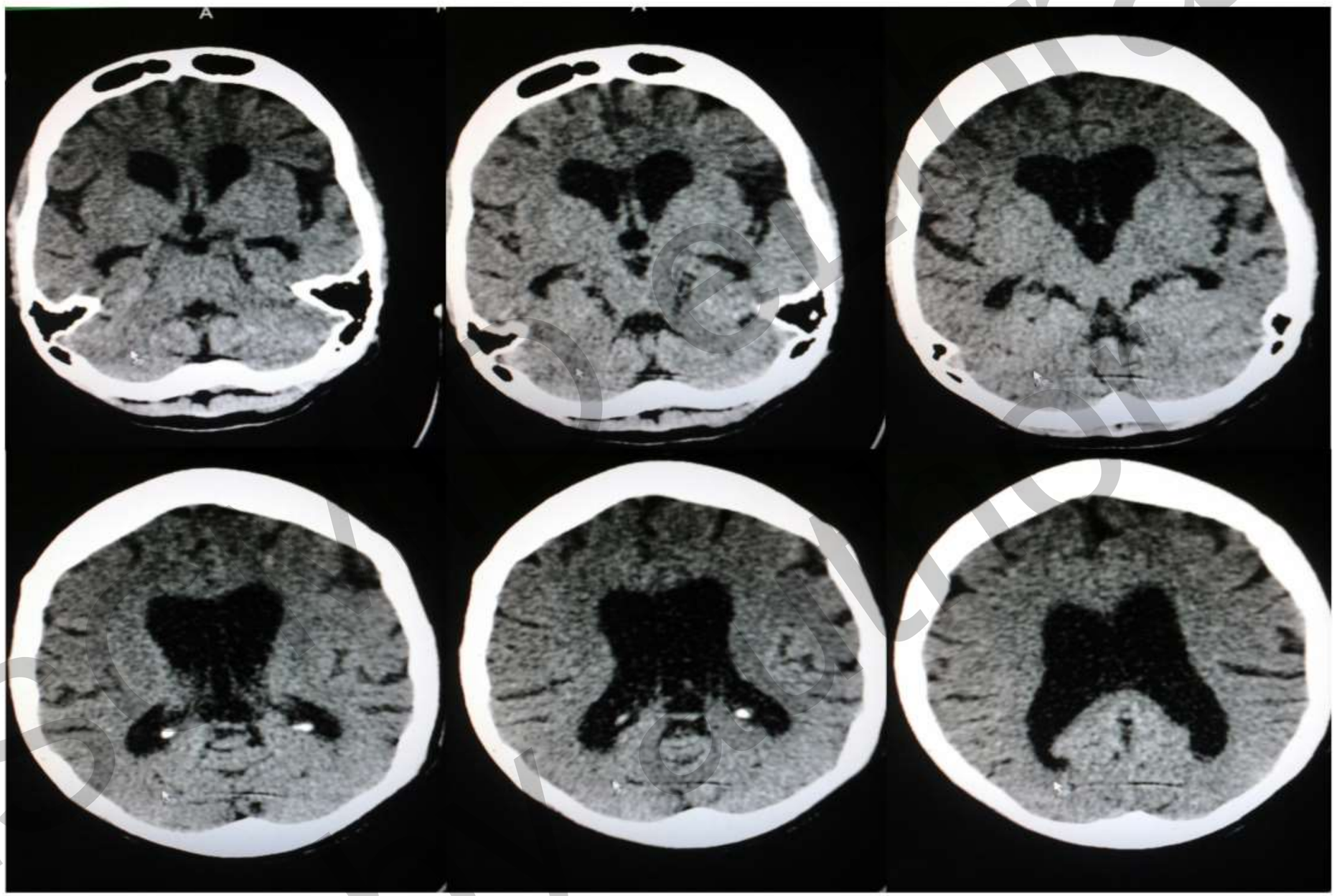
- 30 yo f, fever, vomiting, diarrhea, muscle + joint pain, HA x 7 days
- Rx po artesunate-amodiaquine, amoxacillin, paracetemol, multivitamins, metoclopramide, ORS blood EBOV PCR+ day 8
- Vomiting- IV Ceftriaxone, Artesunate, Ringer's Lactate
- Day 13-15 improved walking on ward, talking with other patients.
- Day 20 Neurologic deterioration "unconscious"
- Retreated IV Ceftriaxone and Artesunate
- No improvement in MS- blood PCR (-), transferred to hospital,IV Fluconazole added
- Exam afebrile, stiff neck, GCS 9/15 (E3,V1,M5) symmetric neuro exam
- Fluctuating MS, polyarthritis joint PCR (-) Rx IM prednisone
- Persistent depressed MS CSF EBOV PCR (+) Day 40 / blood (-); OP 30; CT- performed
- Neuro improvement 14/23 MMSE
- PCR (+) sweat, urine
- D/C Day 50 Day 64 joint pain, dizziness, slow affect + memory urine +

EBOV NA in body fluids
based on Cycle Threshold Detection

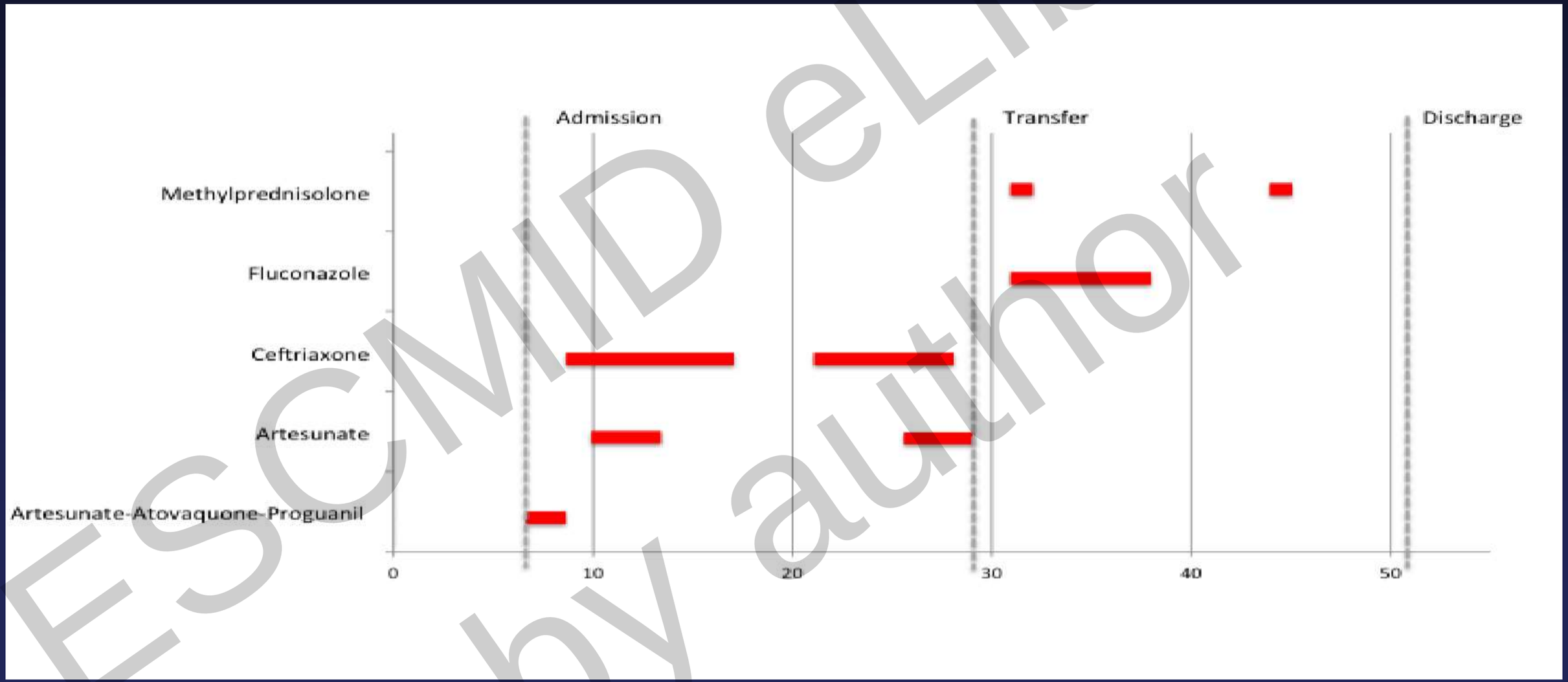


Altona RealStar Filovirus Screen kit Altona Diagnostics, Germany

Howlett P et al EID 2016



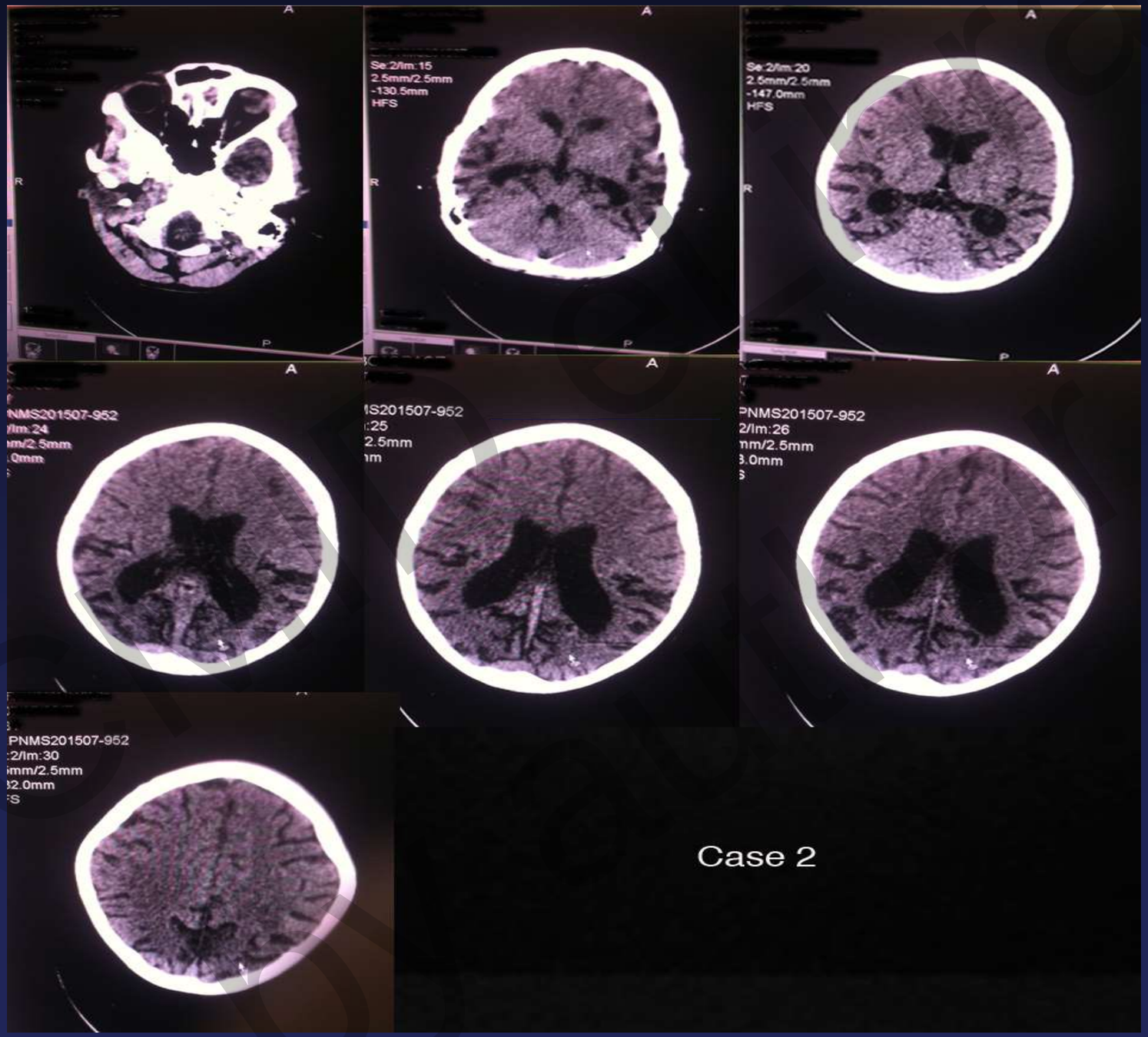
Summary of Care at Ebola Holding/Treatment Unit and Connaught Hospital



Howlett P

Case 2

- 8 yo f previously normal; never recovered from Ebola 4 mo earlier
- Had remained blind, incontinent, unable to follow commands, verbal output was incomprehensible sounds, yet walked well with assistance
- CSF WBC 3 (55P 45L) glucose 1.3 protein 16.8 g/dl gm stain and AFB (-)
- seizures


Se:2/Im:15
2.5mm/2.5mm
-130.5mm
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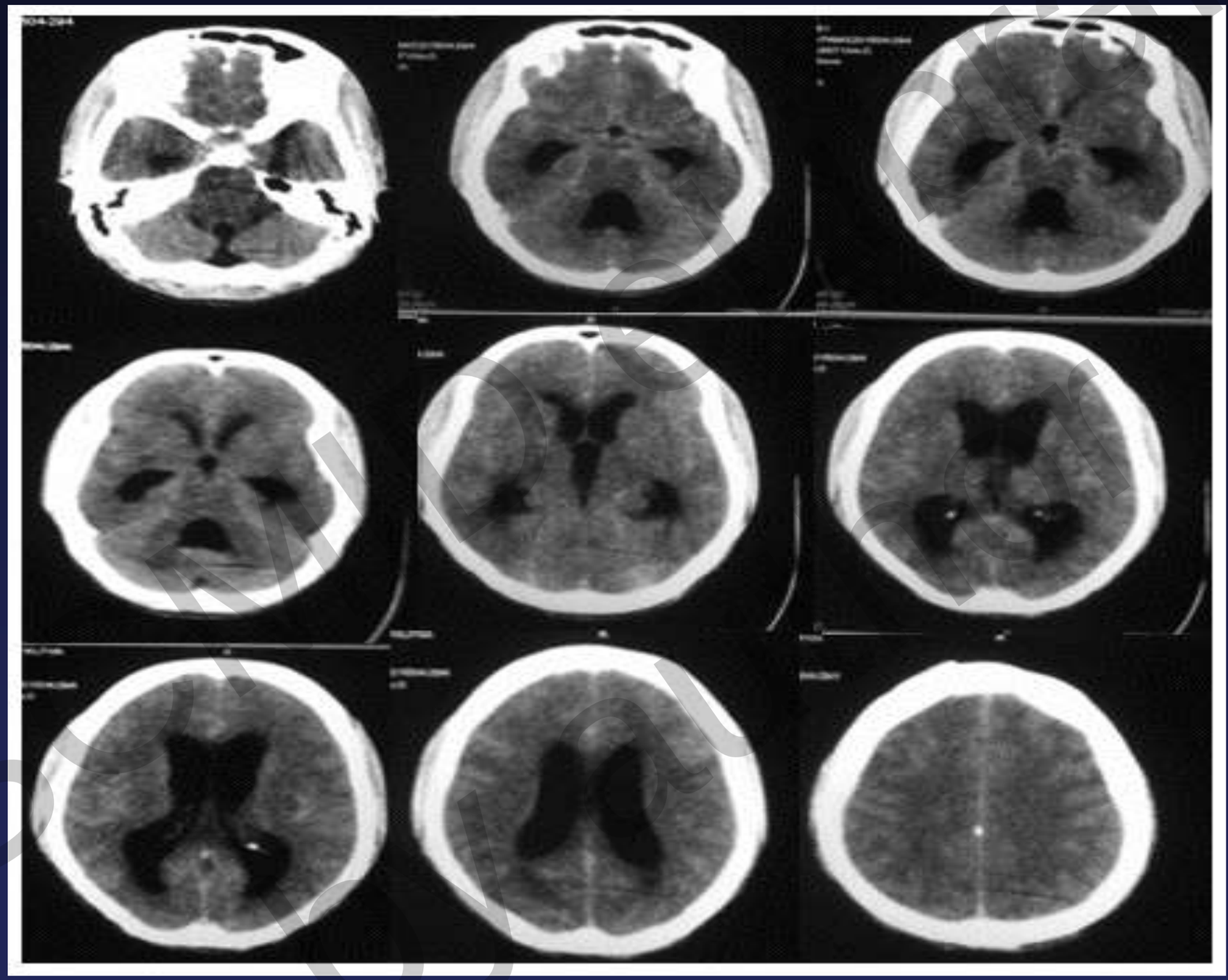
Se:2/Im:20
2.5mm/2.5mm
-147.0mm
HFS
PNMS201507-952
2/Im:26
nm/2.5mm
3.0mm
Case 2

Case 3

- 32 yo m, 4 weeks after clearing Ebola from serum, developed fevers and coma, and expired



Summary: Ebola-Associated Neuro Cases

- 3 cases
- Case 1: 30 yo, day 20, impaired level of consciousness associated with confirmed EBOV nucleic acid in CSF, at time blood was PCR(-)
  - + CSF PCR signifies active infection
  - Pt improved but had some sequelae, and steroids did no harm.
  - Meets criteria for post-Ebola syndrome, & got there via encephalitic illness of 3-4 wks duration produced global brain atrophy.
  - Multi-organ virus persistence-persistence may be indicator or risk factor for CNS invasion
  - Some analogies to eye disease (presence of virus + immune response)
- Case 2: 8 yo poor neurologic status since Ebola,
  - severe but atypical sequelae (sparing motor systems by report), associated with atypical (caudal) brain atrophy
- Case 3: 32 yo Neurologic death 4 wk after Ebola
  - Malignant appearing CT scan

Consider brain in therapeutic decisions

outcome will require understanding virologic + inflammatory cxs in multiple organs

Staging criteria includes Neuro status

Clinical staging system for Ebola virus disease used at Kerry Town Ebola treatment centre and subsequent standard clinical management

	Clinical features	Typical patient	Standard treatment
Stage 1: early or mild	Non-specific features: pyrexia, weakness, lethargy, myalgia, and arthritis	Ambulatory, able to compensate for fluid losses via oral intake	Oral rehydration solution, symptomatic treatment, zinc or multivitamins, antimalarials if rapid malaria diagnostic test-positive, targeted electrolyte replacement *, treatment of hypoglycaemia
Stage 2: gastrointestinal involvement	As above plus: diarrhoea, vomiting or abdominal pain, or both	Unable to compensate for fluid losses via oral intake due to emesis or loss of large volumes	As per stage 1, plus: Intravenous fluid treatment (3000–6000 mL/24 h for adults, guided by fluid and electrolyte balance), intravenous ceftriaxone †
Stage 3: complicated	As above plus: haemorrhage, shock, neurological involvement, or signs of organ failure	Critically ill, usually hypovolaemic, often with confusion or seizures, bleeding	As per stage 1 + 2, plus: As clinically indicated: sedation or antiepileptics, vitamin K, and fresh frozen plasma ‡

Neurology = critical illness

Hunt et al. Lancet ID 2015

But exceptions

Host and Virus Factors as Disease Determinants

- CNS Immune Privilege is Incomplete
- Range of Inflammatory or Degenerative sequelae are seen
- Onset? Case1:Neuro illness declares itself at 3-4 weeks; C3:4 wks p clearing
- Pantropic virus
  - Gains access through infected monocytes, vascular endothelial cells, choroid plexus
- Encountering Primed, Recovering or Restored immune response
- Quality and timing of immune response a determinant of survival and neuropathology

Virus

- Receptor usage (Tissue and Species Tropism) has unique relation to CNS
  - Ebola uses several different moieties to bind cell surfaces (C-type lectins, folate receptor a, Rho GTPases, B1-integrins, glycosaminoglycans, TIM/TAM receptors) but then switches to another receptor requires the late endosomal/lysosomal transmembrane (cholesterol transport) protein Niemann-Pick disease type C1 protein as an internal receptor (Jae and Brummelkamp 2015) (Ezetimibe-cholesterol drug whose target is NPC1)

Host

- Host genetics? Carrier allele frequency for disease-causing mutations > 1:200, larger numbers of non-disease causing variants NPC1.

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Recently Reported EBOV CNS Disease

- Sagui E Janvier F Baize S et al. Severe Ebola virus infection with encephalopathy: Evidence for direct virus involvement. Clin Infect Dis 2015 61:1627-8

  21 yo m, fever, gastroenteritis, HA x 5 days; stiff neck, seizures, coagulopathy treated by plasma transfusion, simultaneous PCR + blood and CSF 24 hr prior to death, day 7 of illness

- Howlett P, Brown C, Helderman T, Brooks T, Lisk D, Deen G, Solbrig M, Lado M. Ebola virus disease complicated by late-onset encephalitis and polyarthritis, Sierra Leone EID 2016 22:150-2

- UK Newspapers and on-line news services

  PC, 39 yo nurse, recovered from Ebola, 9 months later hospitalized with systemic illness and late-stage meningitis

Definitions

- Encephalopathy

"Any disease of the brain" -Stedman's Medical Dictionary

Organic (non-psychiatric) cause of "Altered Mental Status" - operational

Anoxic-ischemic, dialysis, drug-induced, eclamptic, epileptic, Hashimoto, hepatic, hypertensive, toxic-metabolic, mitochondrial, pancreatic, posterior reversible, uremic, Wernicke

non-infectious

good or bad prognosis depending on how got there

- Encephalitis

Infection/Inflammation of the brain

- Meningitis

Infection/Inflammation of membranes of brain or spinal cord, sparing brain parenchyma

Do cases fit the definitions?

- Guinean case- potentially both encephalopathy/encephalitis
- Sierra Leone case- + CSF, altered mental status, and brain injury sequelae
  - Better evidence of direct brain infection- intrathecal EBOV antibodies, isolation of replicating virus, MRI imaging, brain biopsy
  - No CSF cell count, and cannot discount PCR+ products from monocytes in CSF
- UK case
  - Presumed evidence from neurologic exam and MRI that brain itself not infected.

Sierra Leone	UK
Women in 30’s	
Infected in Freetown area Late 2014/early 2015	
Multiorgan disease	
Persistence	
+CSF EBOV PCR	+CSF EBOV PCR
Encephalitis	Meningitis
Treatment: Supportive, hydration, antibiotic, antimalarial	Hyperimmune (convalescent) serum ?Broad Spectrum Antiviral Favipiravir,Brincidofovir, Gilead GS-5734

New / Distinguishing Features of this Epidemic
may be relevant to CNS disease

- More cases
  - Dec 20 2015: 28,637 cases 11,315 deaths (WHO situation report)
- More recovered patients
- More documentation of persistence of infectious virus
- More and varied post-Ebola syndromes
- Less virulent (?)
  - % survivors, NHP studies (contrast Mayinga vs Makona strains, elevated IFNg Marzi 2015) (IFNg neurotoxic e.g. augmenting Alz-type pathology)
- First time in a Lassa-endemic area

New hypotheses, concepts of pathogenesis can be framed and tested,

With goal of linking treatment to molecular, immune, possibly genetic events that affect human response

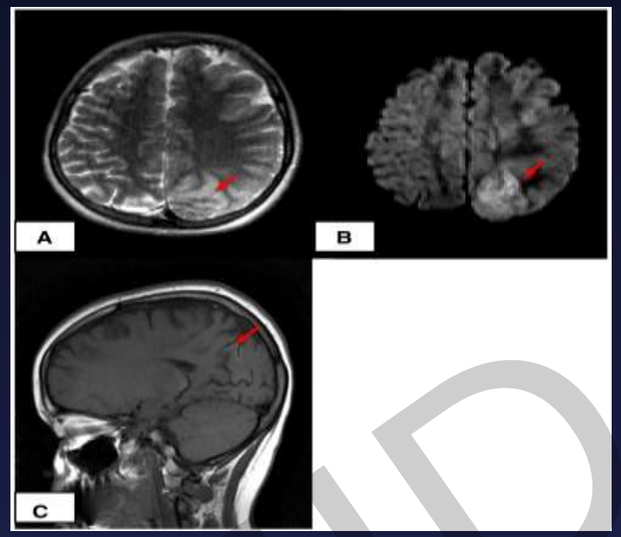
EBOV CNS injury is a consequence of direct and indirect viral effects

- Hypothesis 1: Direct- Viral (neuropathology, pantropism)

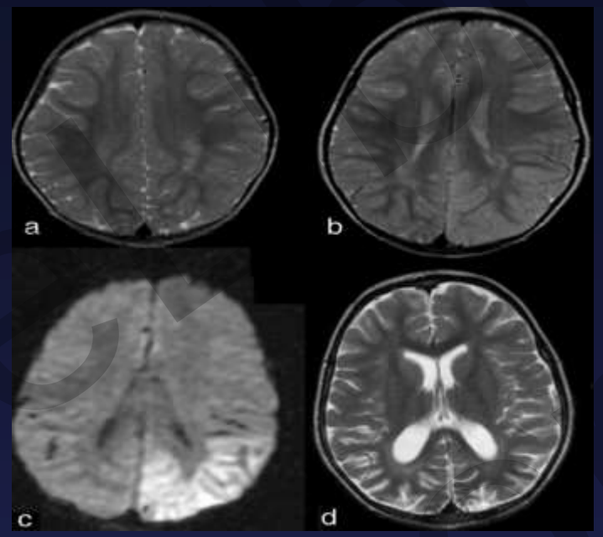
- Hypothesis 2: Indirect- Immune (CNS inflammation as in cases)
- Hypothesis 3: Indirect- Bioenergetic Demands or Mitochondrial Dysfunction

Occipital, Parieto-Occipital Focality

PolG1

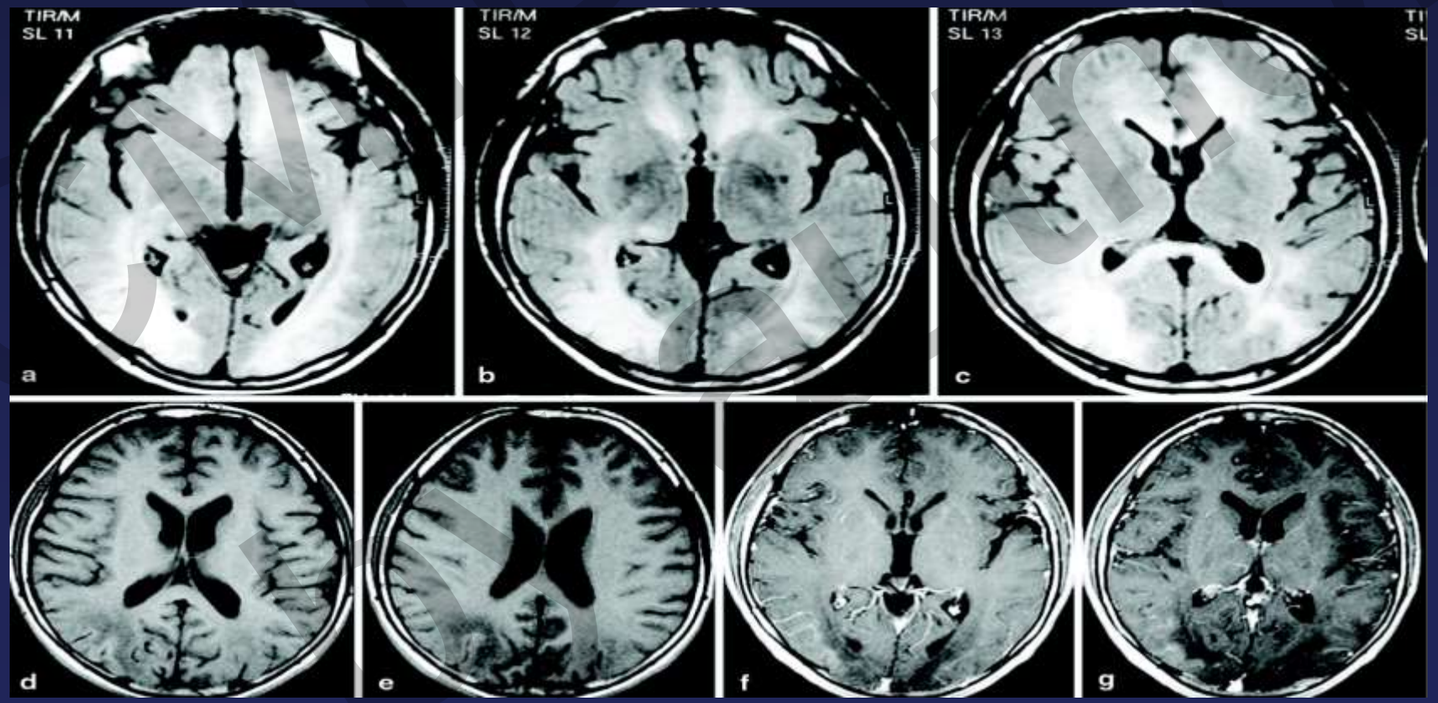


Roshal et al Epilepsy & Beh 2011



Sofou et al Mitochondrion 2013

SSPE



Dundar et al Clin Neuroradiol 2014

Do mitochondria matter?

- Testable with functional assays of electron transport chain activities of accessible tissues

Yes, if innate immunity is a mitochondrial function.

- Mitochondria function as signaling platforms in the innate immune response (mtDNA stress is a cell-intrinsic trigger of antiviral signaling)
  - West AP et al. Mitochondrial DNA stress primes the antiviral innate immune response. Nature 2015 520:553-7
  - Kugelberg E Innate immunity: Stressed mitochondria provide protection. Nat Rev Immunol 2015 15:134
  - White MJ, Kile BT. Stressed mitochondria sound the alarm (mtDNA stress triggers interferon production) Immunol Cell Biol 2015 93:427-8

- Mitochondria have a role in nucleoside analogue toxicity (AZT-induced muscle disease)

“Learn from the bats”

- Bats are special as reservoirs for emerging viruses
- Because they are flying mammals
- Bats tolerance of otherwise virulent viruses has depended on evolution of efficient mitochondrial mechanisms
- Bats have evolved intracellular mitochondrial adaptations to minimize oxidative stress during metabolically costly activities such as flight
- And Bats immune system interprets intracellular pathogen infection in a manner similar to oxidative damage

  - Wang LF et al. Mass extinctions, biodiversity and mitochondrial function: are bats ‘special’ as reservoirs for emerging viruses? Curr Opin Virol 2011 1:649-57
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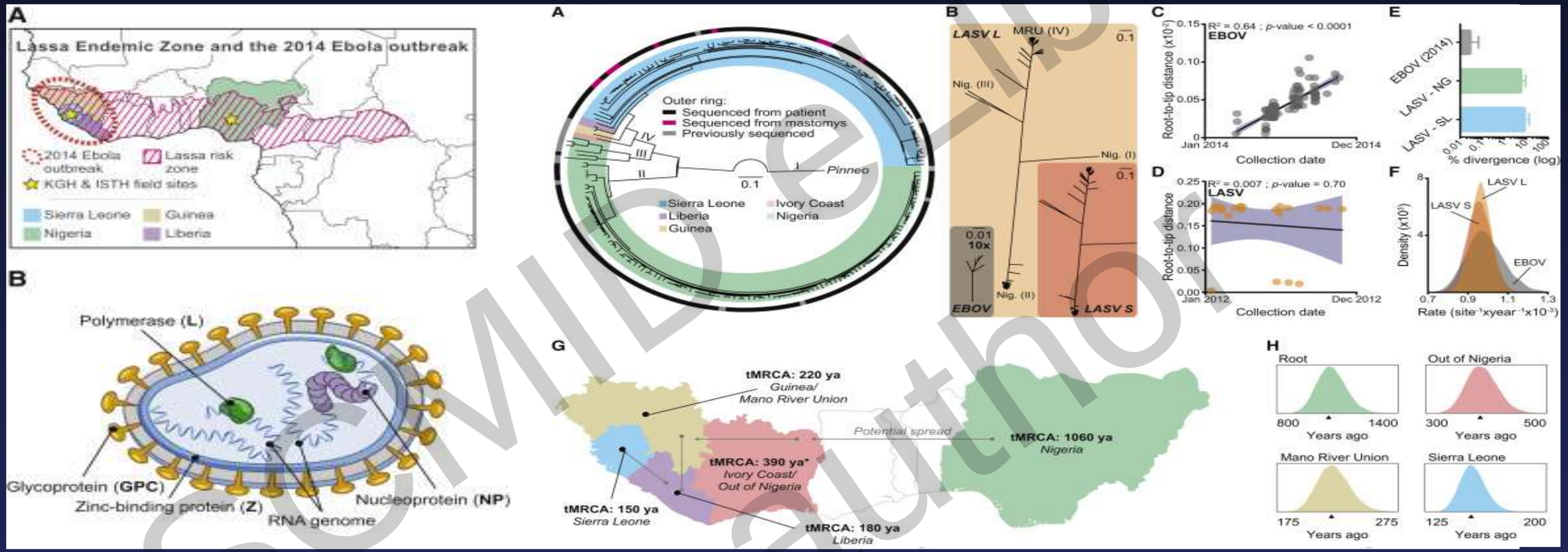
  - Brook CE, Dobson AP. Bats as ‘special’ reservoirs for emerging zoonotic pathogens. Trnds Microbiol 2015 23:172-80

Ebola in a Lassa endemic area: Another form of Antiviral Priming?



- Consolidation of Fig 1, Lassa endemic zone of West Africa, and Fig 2, estimates of antiquity of Lassa in W Africa, from Anderson KG et al. Cell 162 738-750 2015

Consequences for Acute Management

- Antiviral/Supportive Treatment with Dx
- Establish if encephalopathy or encephalitis (CSF, imaging studies)
- Altered Mental Status in absence of evidence of CSF, CNS virus is an Encephalopathy……For which reversible causes are sought
- If Ebola is found in an abnormal (nonclassical) location, e.g. eye and brain, there is possibly a pathogenic inflammatory component
- Specific Antiviral + immune therapy (awaits a more profound understanding of viral, immune and cytokine dynamics)
- For now, Well-timed steroids in suitable patients can be useful
- Consider any known g x e interactions or clues from genetics in treatment plan

Post-Script to the Epidemic

- For the first time in Ebola's history, Neurologic complications themselves are the subject of multiple manuscripts and studies.
- This epidemic has introduced or expanded concepts of sequestration, persistence, reactivation, not usual topics in Ebola.
- Neuro sequelae raise the possibility of CNS immune-mediated toxicity as a mechanism of toxic encephalopathy, global cerebral atrophy, or meningitis.
  - Who should get immunomodulatory treatment and when?
  - Baize S et al. Clin Exp Immunol 2002 128:163-8, Wauquier N et al. PLOS Trop Dis 2010 4(10):e837
- Neuro sequelae raise the possibility of other pathogenic mechanisms, such as mitochondrial dysfunction.
  - "Mitochondrial cocktails" as adjuvant treatment?
- And promotes consideration of bringing aspects of genetics to clinical trials: NPC1 or mitochondrial genetics?

Ongoing Survivor Studies focused on CNS Disease

- PREVAIL III Ebola Natural History Study: NIH study in Liberia of long-term health consequences of EBV infection, examining prevalence of eye, musculoskeletal, and neurological disease and immune characteristics of these patients *ClinicalTrials.gov*

- EBOV Survivors Study in Sierra Leone: Kings Sierra Leone Partnership and Connaught Hospital characterizing neurological and psychiatric disease in EBOV survivors

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